DATA EVALUATION RECORD

MANDIPROPAMIDE (NOA 446510)

Study Type: OPPTS 870.3800 [§83-4]; Multigeneration Reproduction Study in Rats

Work Assignment No. 4-1-121 G; formerly 3-1-121 G (MRIDs 46800230 and 46800231)

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DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study - [rat]; OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 036602 **DP BARCODES:** D328539
TXR#: 0054273

TEST MATERIAL (PURITY): NOA 446510 (96.5% w/w)

SYNONYMS: Mandipropamid; 4-chloro-*N*-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)benzeneacetamide

CITATION: Milburn, G.M. (2005) NOA446510: Multigeneration reproduction toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Project ID.: Report No.: RR0990-REG, Syngenta No.: T005169-01, November 11, 2005. MRID 46800230. Unpublished.

Lees, D. (2005) NOA446510: Preliminary one generation reproduction toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Project ID.: Report No.: RR0964, Syngenta No.: T004587-02, December 20, 2005. MRID 46800231. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (MRID 46800230), Mandipropamid (96.5%; Batch # SEZ2BP007) was administered in the diet to 26 Alpk:AP$_f$SD (Wistar-derived) rats/sex/dose group at dose levels of 0, 50, 250, or 1500 ppm (mg/kg/day mean of F0 and F1 premating M/F = 0/0, 4.7/5.0, 22.9/24.5 and 146.3/148.2). The P generation animals were fed the test diets for 10 weeks prior to mating to produce the F1 litters. Upon weaning, F1 parents were fed the test diets for 10 weeks prior to mating to produce the F2a litters. Because of equivocal differences in live birth index, whole litter losses, and live litter size between the control and 1500 ppm groups, the F1 parents were mated a second time to produce the F2b litters.

There were no effects of treatment on parental mortality, clinical signs, estrous cycle duration or periodicity; sperm parameters, or gross pathology. Additionally, there were no treatment-related effects on body weights, body weight gains, food consumption, or food utilization during gestation or lactation.

During pre-mating in the P generation, food consumption was increased by 5-10% (p<=0.05) in the 1500 ppm males during Weeks 1-4, while body weights were comparable to controls. Because these animals were eating more food to maintain the same body weight, food utilization was decreased (p<=0.05) by 8% during Weeks 1-4, resulting in decreased (decr. 4%; p<=0.01) food utilization for the overall (Weeks 1-10) pre-mating period.

At 1500 ppm in the F1 generation, body weights were decreased by 2-8% in the males throughout pre-mating, attaining significance (p<=0.05) in 7 of 11 weeks. Weekly cumulative body weight gains in these animals were decreased by 6-9% (p<=0.05) throughout pre-mating, resulting in a decrease of 6% in body weight gain for the overall (Weeks 1-11) pre-mating period. Food consumption in these males was decreased by 5% during Weeks 9-10, and food utilization was decreased by 8% (p<=0.01) during Weeks 1-4 and by 6% (p<=0.05) during Weeks 5-8, resulting in a decrease of 4% (p<=0.01) for overall (Weeks 1-10) food utilization.

In the 1500 ppm F1 females, food utilization was comparable to controls during pre-mating. Thus, the increases in body weights and body weight gains observed in these dams were not considered adverse and may have been due to the increased food consumption.

At 1500 ppm, absolute and adjusted liver weights were increased in the P males (incr.17-19%) and females (incr.7-8%) and in the F1 males and females (incr.11-17%). These increases attained significance (p<=0.05) except for the absolute liver weight in the P females. Because there were no microscopic findings in the liver and clinical chemistry analyses were not performed, the increased liver weights were considered equivocal in this study. Similar findings in the liver were noted in the subchronic (MRID 46800216) and combined chronic/oncogenicity (MRID 46800234) studies in rats, submitted concurrently.

Absolute and adjusted adrenal weights were increased by 13-23% (p<=0.05) at 1500 ppm compared to controls in the P males and F1 males and females. Absolute adrenal weights were also increased (incr.11%; p<=0.05) in the 250 ppm F1 females. An increased severity of vascular ectasia was observed in the 1500 ppm females (8 dams with minimal to moderate severity) compared to controls (7 dams of minimal severity). However, vascular ectasia was only observed in 0-4 animals per group at 1500 ppm in the P generation male and females and in the F1 generation males. The Sponsor stated that vascular ectasia in the adrenal is a common spontaneous age-related lesion seen predominantly in female rats. It was also stated that the severity and incidence observed in the 1500 ppm F1 dams is within the historical control maximum for 1 year interim sacrifice. Although data were not available, it was stated that the incidence of this finding can be as high as 90% at one year and varies widely, along with severity. Therefore, the findings in the adrenal gland were considered to be equivocal.

The LOAEL for parental toxicity is 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females) based on decreased body weights, body weight gains, food consumption, and food utilization in the males. The NOAEL is 250 ppm (equivalent to 22.9/24.5 mg/kg/day in males/females).

There were no treatment-related effects on viability, clinical signs, or anogenital distance. In the

F2a litter, the live birth index was lower at 1500 ppm (86.8%) compared to controls (97.7%), and the litter size on PND 1 was decreased by 22% ($p<=0.01$) at 1500 ppm compared to controls. However, when the numbers of whole litter losses were excluded, these effects were not evident. At 1500 ppm, adjusted pup weights were decreased ($p<=0.05$) by 7-14% in the F1 and F2b pups of both sexes. In the F2a litter, pup weights of the treated males and females were comparable to controls. There were no effects of treatment on total litter weight.

In the F1 parental males, the time until preputial separation was longer ($p<=0.05$) at 1500 ppm (44.8 days) compared to controls (43.7 days), indicating a slight delay in sexual maturation likely related to the decreased pup body weights beginning on PND 15. However, the time to vaginal opening was unaffected by treatment.

At 1500 ppm, adjusted (for terminal body weight) liver weights were increased by 9-17% in the F1, F2a, and F2b pups. Additionally at this dose, absolute liver weights were increased by 14% in the F2a females. However, because no clinical chemistry or histopathology analyses were performed, the increased liver weights were considered equivocal.

The LOAEL for offspring toxicity 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females) based on decreased pup body weights in both sexes. The NOAEL is 250 ppm (equivalent to 22.9/24.5 mg/kg/day in males/females).

There were no effects of treatment on the pre-coital interval, number of females pregnant, number of complete litter resorptions, mating success, post-implantation loss, or gestation duration in either generation. There were no effects of treatment on whole litter losses in the P generation. However, in the F1 generation, the number of whole litter losses was increased in the F2a litter at 1500 ppm compared to controls. Therefore, the F1 dams were mated a second time to produce the F2b litters, and there was no effect on the number of whole litter losses, indicating that the finding in the F2a litter was incidental.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

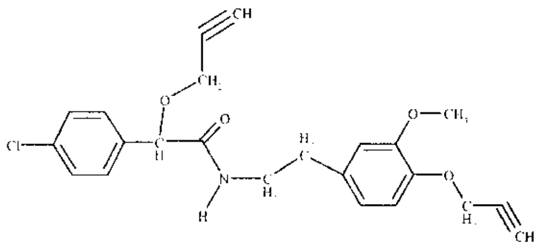
<u>COMPLIANCE</u>: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Mandipropamid Technical

Description:	Slightly beige solid
Lot/batch #:	SEZ2BP007
Purity:	96.5% a.i.
Compound stability:	The test substance was stable in the diet for up to 42 days at room temperature
CAS # of TGAI:	374726-62-2
Structure:	



2. **Vehicle:** Diet

3. **Test animals**

Species:	Rat
Strain:	Alpk:AP_fSD (Wistar-derived)
Age at study initiation:	Approximately 5 weeks (35 days)
Weight at study initiation:	136-197 g, males; 112-159 g, females
Source:	AstraZeneca Biological Services Section, Alderly Park, Macclesfield, Cheshire, UK
Housing:	After assignment and during the pre-mating period, parents were housed in same-sex pairs with 2 males or 2 females from the same litter in a cage. Males and females from the same group were housed in adjacent cages during this time to avoid anestrous. During mating, animals were housed in pairs (1 male: 1 female). Females were housed individually during gestation and with their litters during lactation.
Diet:	CT1 diet (Special Diets Services Ltd, Stepfield, Witham, Essex, UK), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature** 22 ± 3°C **Humidity** 30-70% **Air changes** At least 15/hour **Light cycle** 12 hours light/12 hours dark
Acclimation period:	Approximately two weeks

B. PROCEDURES AND STUDY DESIGN

STUDY DATES: Initiation date: June 12, 2003 (protocol signed); experimental start date: June 23, 2003 (first data collected); experimental termination date: March 9, 2005 (pathology report signed).

1. **Mating procedure:** One female was paired with one male from the same dose group for a maximum of 14 days. This was accomplished by replacing one male with one female

belonging to the same group from an adjacent cage. Sibling mating was avoided. However, one P generation sibling mating per group occurred by mistake; no F1 animals were selected from any of the ensuing litters. Vaginal smears were taken daily and examined for positive evidence of mating as indicated by the presence of sperm. The day on which positive evidence of mating was detected was designated as gestation day (GD) 1. Females with positive evidence of mating were separated from the male and housed individually. During the mating period to produce the F2b litters, F1 parents were paired with different partners from the first mating.

2. **Study schedule:** The P generation animals were fed the test diets for 10 weeks prior to mating to produce the F1 litters. The performing laboratory stated that in their experience, a compound-related reduction in body weight can affect survival if the pups are weaned at post-natal day (PND) 22. Thus, F1 weanlings were selected on PND 29 to be parents and were fed the same test diet concentration as their dam for 10 weeks prior to mating to produce the F2a litters. Because of equivocal differences in live birth index, whole litter losses, and live litter size between the control and 1500 ppm groups, the F1 parents were mated a second time to produce the F2b litters.

3. **Animal assignment:** The animals were housed in five racks in thirteen replicates (randomized blocks). Each replicate consisted of 2 rats/sex/group. The P animals were randomized by litter prior to the start of the study to ensure that littermates were evenly distributed across the dose groups. Litters were randomly allocated to the replicates, and animals within each litter were randomly selected and assigned to the test groups shown in Table 1.

TABLE 1. Animal assignment [a]					
Test group	Dose (ppm) [b]	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	26	26	26	26
Low (LDT)	50	26	26	26	26
Mid (MDT)	250	26	26	26	26
High (HDT)	1500	26	26	26	26

a Data were obtained from page 27 of MRID 46800230.
b Exposure to the test substance was continuous throughout the study.

4. **Dose-selection rationale:** Doses for the current study were selected based on the results from a one-generation range-finding reproduction toxicity study in rats (MRID 46800231). This study was concurrently submitted, and a summary is included in an appendix to this DER.

5. **Dosage preparation and analysis:** Test diets were prepared for each dose group by mixing the appropriate amount of the test substance with 1 kg of milled diet to achieve a pre-mix. Each pre-mix was then mixed with 59 kg of additional diet to achieve the desired concentration. Prepared diets were stored in glass jars for up to 42 days at room temperature. From the first batch, all dose levels were analyzed for concentration, and homogeneity (top, middle, bottom) was verified in the 50 and 1500 ppm diets. Thereafter, concentration

analyses were performed on each dose level at approximately 2-month intervals. Stability of the test substance in the diet was demonstrated at room temperature at 50 ppm in a concurrently submitted combined chronic/oncogenicity study (MRID 46800234) and at 100 and 10,000 ppm in a separate study (CTL Study # WK0441). Stability was verified for up to 42 (50 ppm), 48 (100 ppm), or 44 (10,000 ppm) days.

Results

Homogeneity: 106.2-109.4% nominal; -1.3 to 1.7% deviation; 0.41-1.52% C.V.

Stability: 97.3-103.5% of initial concentration

Concentration: 98.4-107.6% nominal

The analytical data indicate that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** The test material was administered in the diet continuously throughout the study (i.e., P generation adults were fed the test diets *ad libitum* beginning 10 weeks prior to mating, and the selected F1 adults were fed the same test diet concentrations as their parents beginning on PND 29).

C. OBSERVATIONS

1. **Parental animals:** All rats were examined twice daily for mortality and changes in clinical condition and behavior. Detailed examinations were performed at the same time that body weights were recorded. Body weights of the males were recorded weekly throughout the study. For the females, body weights were recorded: weekly during the pre-mating period; on GD 1, 8, 15, and 22; and on lactation day (LD) 1, 5, 8, 15, 22, and 29. Additionally, the body weight of each rat was weighed at termination. Food consumption was recorded continuously and was calculated, at weekly intervals, as a mean value (g food/rat/day) for each cage (n = 13) for the males and females throughout the pre-mating period and additionally for the females throughout gestation and lactation. However, food consumption was not measured for the F1 dams during the gestation and lactation periods of the F2B litters. Food utilization for each cage, calculated as the body weight gained by the rats in each cage per 100 g food eaten, was reported for Weeks 1-4, 5-8, 9-10, and for the overall (Weeks 1-10) pre-mating period. Estrous cycle periodicity and duration were determined from vaginal smears taken daily beginning 3 weeks prior to mating. Sperm motility, enumeration, and morphology were determined from the P and F1 parental males surviving to scheduled termination. Sperm motility (i.e., straight line, curvilinear, and average path velocity) and sperm enumeration (i.e., total and static counts) were examined in all dose groups. Additionally, the numbers of homogenization-resistant spermatids were counted in the control and high dose groups. Sperm morphology assessment consisted of classifying, as either normal or abnormal, at least 200 spermatids per slide from 2 slides per animal from the control and high dose groups. Abnormal sperm were categorized according to head (detached, double, abnormal shape, abnormal size, or abnormal acrosome), tail (double,

coiled/kinked or abnormal size), or multiple (head and tail abnormalities).

2. **Litter observations:** The following litter parameters (X) were recorded in all F1a, F2a, and F2b litters (Table 2):

TABLE 2. F_1 / F_2 Litter Observations [a]						
Observation	Time of observation (lactation day)					
	Day 1	Day 5	Day 8	Day 15	Day 22	Day 29
Number of live pups	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X
Pup weight	X	X	X	X	X	X
Sex of each pup (M/F)	X	X	X	X	X	X
External alterations	X	X	X	X	X	X
Anogenital distance [b]	X					

a Data obtained from pages 29-30 in MRID 46800230.
b Recorded for F2a and F2b litters (but not for F1 litters or pups found dead)

Litters were examined for dead or moribund pups at least once daily, and any such pups were subjected to a gross necropsy. Litters were not standardized (i.e., no pups were culled on PND 5).

Sexual maturation was determined for all F1 parents. Daily checks were made for vaginal opening beginning on PND 29 and for preputial separation beginning on PND 39. Body weight and any clinical observations were recorded on the day on which criterion was achieved.

3. **Postmortem observations**

a. **Parental animals:** Dams euthanized prior to scheduled termination were killed by overexposure to halothane Ph. Eur. vapor followed by exsanguination for the following reasons: (i) observations of prolonged gestation or dystocia; (ii) failure to litter by nominal GD 25; or (iii) total litter loss. Parental rats surviving to scheduled termination were similarly killed, with males being euthanized after completion of the mating period and females terminated on or soon after PND 29. These animals, along with any found dead, were subjected to a gross necropsy

From the animals surviving to scheduled termination, the following checked (X) tissues were collected, and it was stated that they were preserved in an appropriate fixative. Additionally, the (XX) organs were weighed:

XX	Adrenal glands	XX	Epididymides	XX	Ovaries
XX	Brain [a]	XX	Seminal vesicles [b]	XX	Uterus [c]
XX	Kidneys [a]	XX	Prostate gland [b]	XX	Oviducts [c]
XX	Liver	XX	Coagulating gland [b]	XX	Cervix [c]
XX	Pituitary gland	XX	Testes	X	Vagina
XX	Spleen [a]			X	Mammary gland (females)
XX	Thyroid [a]				
X	Gross lesions				

a Preserved and stored but not examined.

b The seminal vesicles were weighed with the prostate and coagulating gland. The weight of the seminal vesicles was derived by subtracting the prostate weight from the combined weight of the prostate and seminal vesicles.

c The uterus was weighed with the oviducts and cervix.

With the exception of the brain, kidney, spleen and thyroid, the tissues listed above from the control and high dose animals were processed routinely, embedded in paraffin, sectioned at 5μm, stained with hematoxylin and eosin, and examined microscopically. Additionally, tissues from animals of suspected fertility and the adrenal glands from females were examined in the intermediate dose groups. The number of primordial follicles was counted for the F1 females from the control and high dose groups.

b. **Offspring:** Any pups requiring euthanasia prior to scheduled termination were killed by overexposure to halothane Ph. Eur. vapor followed by exsanguination. These animals, along with any decedents, were subjected to a gross necropsy and then discarded.

Among pups surviving to scheduled termination, the F1 offspring not selected as parental animals and all F2 offspring were killed at 29 days of age. The brain, spleen, thymus, and liver were weighed from one pup/sex/litter from all litters surviving to scheduled termination. Three pups/sex/litter (when litter size permitted) were randomly selected from each dose group for macroscopic examination; and tissue samples from brain, spleen, thymus, liver, and any gross lesions were collected and preserved, but were not examined microscopically.

D. DATA ANALYSIS

1. **Statistics:** The following statistical procedures were used:

Parameter	Statistical procedure
Parental and pup body weights (except initial weights)	Analysis of covariance (ANCOVA), using initial body weight as the covariate, followed by pair-wise comparisons of treated groups with controls using a two-sided Student's t-test
Initial parental body weights (including gestation and lactation) Food consumption Food utilization Sperm velocities, straightness, and count Number of implantations Number of live plus dead pups on Day 1 for each dam Litter size Gestation duration Pre-coital interval Total litter weight Estrous cycle duration and #cycles/female during pre-mating Day of preputial separation or vaginal opening Initial pup body weight Anogenital distance	Analysis of variance (ANOVA), followed by pair-wise comparisons of treated groups with controls using a two-sided Student's t-test
Sperm parameter percentages (i.e., % motile, normal, abnormal, etc.) Percentages of: post-implantation loss pup survival pup sex ratio	Double arcsine square root transformation of Freeman and Tukey, followed by ANOVA and pair-wise comparisons of treated groups with controls using a two-sided Student's t-test
Parental and pup organ weights	ANCOVA adjusting for terminal body weights and ANOVA, each followed by pair-wise comparisons of treated groups with controls using a two-sided Student's t-test
Proportions of: successful mating whole litter losses litters with gestation length of ≤22, 22, or ≥22 days litters with pre-coital interval of 1, 2, 3, 4, or ≥4 days females with 3, 4, 5, or 6 estrous cycles F1 animals with observed sexual maturation on each day litters affected by post-implantation loss litters with all pups born live litters with all pups surviving	Fisher's exact test
Number of primordial follicles	Square-root transformation followed by ANOVA and pair-wise comparisons of treated groups with controls using a two-sided Student's t-test

Statistical significance was denoted at $p \leq 0.05$ and 0.01. Although relative (to body weight) organ weights were presented, these data were not analyzed statistically because the adjusted values were considered to be more appropriate. Analyses of parental body weights and food consumption during lactation excluded whole litter losses. Analyses of live born pups, litter size, and pup survival were presented both including and excluding whole litter losses. ANOVA and ANCOVA allowed for the replicate structure in the experimental design. Before proceeding with parametric analyses, the assumption of normal distribution of the data should have been verified. Otherwise, the statistical methods were considered appropriate.

2. **Indices**

Reproductive indices: The following reproductive/viability indices were calculated by the performing laboratory from breeding and parturition records of animals in the study:

Mating success (%) = # dams producing a viable litter (i.e., at least one pup found alive at PND 1)/ total # dams x 100

Gestation duration = # days from the date of positive vaginal smear to date of birth (but only in females fulfilling the criterion for successful mating listed above)

Pre-coital interval = # days between the dates of pairing and the positive vaginal smear.

Offspring viability indices: The following viability indices were calculated by the performing laboratory from lactation records of litters in the study:

Live birth index (%) = # live pups/total # pups born x 100

Viability indices = # pups surviving to PND 5, 8, 15, 22, or 29/total # pups born x 100

3. **Historical control data**: Not provided.

II. RESULTS

A. PARENTAL ANIMALS

1. **Mortality and clinical signs**

a. **Mortality**: There were no treatment-related mortalities. In the P generation, the following three males were killed due to clinical signs/humane reasons: (i) 250 ppm male #70 during Week 20 due to circling behavior and piloerection; (ii) 1500 ppm male #85 during Week 16 due to a subcutaneous mass; and (iii) 1500 ppm male #98 during Week 20 due to a bulging eye. Several P generation females were killed for investigation because they did not litter, including animals in the control (3 rats), 50 ppm (8 rats), 250 ppm (1 rat), and 1500 ppm (4 rats) groups; however, these incidences did not occur in a dose-related manner.

In the F1 generation, the following mortalities were noted: (i) a 50 ppm male (#148) was found dead during Week 25; (ii) a 250 ppm male (#61) was killed during Week 14 following clinical signs of scabs and wet sores; (iii) a 250 ppm female (#162) was found dead during Week 15; (iv) a control female (#123) was killed for humane reasons following observations of decreased activity, paleness, diarrhea, hunched posture, piloerection, and pinched in sides; (v) a 250 ppm dam (#165) died during difficult parturition of the F2a litter; and (vi) two 50 ppm dams (# 112 and 149) and two 250 ppm dams (#176 and 183) were killed due to difficult parturition during the F2b litter. Several F1 dams were killed for investigation because they did not deliver an F2a litter, including animals in the control (4 rats), 50 ppm (2 rats), 250 ppm (2 rats), and 1500 ppm (7 rats) groups; however, these incidences did not occur in a dose-related manner. All other animals in both generations survived until scheduled termination.

b. **Clinical signs of toxicity:** There were no treatment-related clinical signs.

2. **Body weight, body weight gain, and food consumption**

a. **Pre-mating:** Selected body weight, body weight gain, food consumption, and food utilization data during pre-mating are included in Table 3a. In the P generation, food consumption was increased by 5-10% ($p \leq 0.05$) in the 1500 ppm males during Weeks 1-4, while body weights were comparable to controls. Because these animals were eating more food to maintain the same body weight, food utilization was decreased ($p \leq 0.01$) by 8% during Weeks 1-4, resulting in decreased (↓4%; $p \leq 0.01$) food utilization for the overall (Weeks 1-10) pre-mating period. Body weights, body weight gains, and food utilization in the treated P females were comparable to controls throughout pre-mating; and the only difference in food consumption was an incidental decrease of 7% ($p \leq 0.05$) at 1500 ppm during Week 8.

In the F1 males, minor decreases of 2-8% in body weights were noted at 1500 ppm throughout pre-mating and attained significance ($p \leq 0.05$) in 7 of 11 weeks. Weekly cumulative body weight gains in these animals were decreased by 6-9% ($p \leq 0.05$) throughout pre-mating, resulting in a decrease of 6% in body weight gain for the overall (Weeks 1-11) pre-mating period. Food consumption in these males was decreased by 5% during Weeks 9-10, and food utilization was decreased by 8% ($p \leq 0.01$) during Weeks 1-4 and by 6% ($p \leq 0.05$) during Weeks 5-8, resulting in a decrease of 4% ($p \leq 0.01$) for overall (Weeks 1-10) food utilization.

In the 1500 ppm F1 females, body weights were increased by 3-6% ($p \leq 0.05$) compared to controls beginning at Week 3 and continuing throughout the remainder of the pre-mating period. Weekly cumulative body weight gains in these animals were increased by 6-10% ($p \leq 0.05$) beginning at Week 4 and continuing throughout the remainder of pre-mating, resulting in a increase of 5% in body weight gain for the overall pre-mating period. Food consumption in the 50, 250, and 1500 ppm F1 dams was increased by 8-17% during pre-mating; however, these increases were sporadic and were not dose-related, indicating that they were unrelated to treatment. Food utilization in the treated F1 dams was comparable to controls during pre-mating. Thus, the increases in body weights and body weight gains in the 1500 ppm F1 dams were not considered adverse and may have been due to the increased food consumption.

TABLE 3a. Selected mean (∀SD) body weights (g), body weight gains (g), food consumption (g/animal/day), and food utilization (g food/100 g weight gain) during pre-mating [a]

Observation/study week		Dose Group (ppm)			
		0	50	250	1500
P Generation Males					
Body weight	Week 1	166.5 ± 11.7	167.6 ± 11.2	164.9 ± 13.7	163.0 ± 13.1
Body weight	Week 11	498.4 ± 42.8	512.0 ± 39.8	497.1 ± 44.5	491.1 ± 54.6
Body weight gain	Weeks 1-11	331.9 ± 34.6	344.4 ± 35.8	332.2 ± 37.4	328.1 ± 46.3
Food consumption	Week 1	26.4 ± 2.2	27.2 ± 1.4	27.0 ± 1.6	29.0 ± 2.3** (↑10)
Food consumption	Week 4	32.9 ± 2.0	33.0 ± 1.7	32.4 ± 2.3	34.5 ± 2.8* (↑5)
Food utilization	Weeks 1-4	24.52 ± 0.81	24.29 ± 1.10	24.31 ± 0.71	22.67 ± 1.08** (↓8)
Food utilization	Weeks 1-10	15.40 ± 0.68	15.83 ± 0.74	15.62 ± 0.70	14.72 ± 0.82** (↓4)
P Generation Females					
Body weight	Week 1	137.0 ± 11.4	139.3 ± 11.7	139.9 ± 11.8	137.5 ± 10.5
Body weight	Week 11	282.2 ± 22.0	280.5 ± 22.3	278.8 ± 15.1	278.8 ± 18.9
Body weight gain	Weeks 1-11	145.2 ± 18.0	141.2 ± 19.3	138.9 ± 14.8	141.3 ± 18.3
Food consumption	Week 8	21.8 ± 3.0	21.2 ± 1.8	20.4 ± 1.1	20.2 ± 1.5* (↓7)
Food utilization	Weeks 1-10	9.93 ± 0.67	9.69 ± 0.84	9.78 ± 0.88	9.74 ± 0.85
F1 Generation Males					
Body weight	Week 1	84.7 ± 10.8	85.0 ± 10.8	85.1 ± 11.0	77.6 ± 11.0* (↓8)
Body weight	Week 2 Adjusted	140.8 ± 16.6 138.7	140.4 ± 13.7 138.0	139.8 ± 14.5 137.2	128.6 ± 15.4 135.7* (↓2)
Body weight	Week 11	457.5 ± 41.7	452.0 ± 34.7	456.5 ± 37.3	429.3 ± 39.5
Body weight gain	Weeks 1-11	372.8 ± 34.3	367.0 ± 29.4	371.5 ± 28.2	351.8 ± 32.5* (↓6)
Food consumption	Week 9	29.2 ± 1.4	28.9 ± 1.3	28.5 ± 1.3	27.7 ± 2.4* (↓5)
Food consumption	Week 10	29.9 ± 1.5	29.2 ± 1.2	29.2 ± 1.2	28.3 ± 1.9** (↓5)
Food utilization	Weeks 1-4	33.42 ± 1.27	32.50 ± 2.16	33.21 ± 0.65	30.66 ± 1.27** (↓8)
Food utilization	Weeks 5-8	13.75 ± 1.04	13.80 ± 1.08	14.13 ± 1.35	12.94 ± 0.70* (↓6)
Food utilization	Weeks 1-10	19.61 ± 0.68	19.37 ± 0.89	19.79 ± 0.58	18.77 ± 0.55** (↓4)
F1 Generation Females					
Body weight	Week 1	75.9 ± 8.6	78.8 ± 8.9	79.8 ± 11.6	74.4 ± 8.6
Body weight	Week 3 Adjusted	151.0 ± 14.3 152.7	155.3 ± 10.6 153.3	154.3 ± 17.6 151.0	153.7 ± 14.2 157.4* (↑3)
Body weight	Week 10 Adjusted	248.2 ± 23.4 250.1	255.5 ± 17.9 253.2	255.0 ± 18.8 251.1	259.8 ± 21.8 264.0** (↑6)
Body weight	Week 11 Adjusted	252.5 ± 23.0 254.5	258.0 ± 17.1 255.6	258.3 ± 21.3 254.5	260.5 ± 21.5 264.8* (↑4)
Body weight gain	Weeks 1-11	176.6 ± 17.7	179.2 ± 14.1	178.6 ± 14.2	186.2 ± 18.2* (↑5)
Food consumption	Week 4	18.7 ± 1.6	21.8 ± 2.2** (↑17)	20.1 ± 1.4	21.6 ± 2.7** (↑16)
Food consumption	Week 5	19.2 ± 1.3	20.8 ± 1.5* (↑8)	20.7 ± 1.9* (↑8)	20.8 ± 2.3* (↑8)
Food utilization	Weeks 1-10	13.45 ± 0.76	12.98 ± 0.66	13.13 ± 0.85	13.61 ± 0.85

a Data (n = 26) were obtained from Tables 12 through 15 and 20 through 23 on pages 69-80 and 87-98 of MRID 46800230. Percent differences from controls (calculated by reviewers) are included in parentheses.
* Significantly different from the control group at p≤0.05
** Significantly different from the control group at p≤0.01

b. **Gestation:** There were no effects of treatment on body weights during gestation in either generation (Table 3b). Body weights of the treated dams were comparable to controls in the P generation and in the F1 generation during gestation of the F2a litter. In the F1 generation during gestation of the F2b litter, differences ($p \leq 0.05$) from controls noted in the 250 ppm dams on Day 22 (↑4%) and in the 1500 ppm dams on Day 8 (↓2%) were considered unrelated to treatment because they were minor, transient, and/or unrelated to dose. Body weight gains of the treated groups for the overall (GD 1-22) gestation period were comparable to controls in the P generation and in the F1 generation during the F2a and F2b litters. Food consumption of the treated dams was comparable to controls in the P generation and in the F1 generation during the F2a litter.

TABLE 3b. Selected mean (∀SD) body weights (g), body weight gains (g), and food consumption (g/animal/day) during gestation [a]

Observation/study week		Dose Group (ppm)			
		0	50	250	1500
P Generation					
Body weight	GD 1	284.5±21.4	280.3±17.5	278.4±17.1	276.5±19.5
Body weight	GD 8	310.0±18.3	306.4±17.2	305.0±17.3	307.9±19.2
Body weight	GD 15	342.4±17.6	338.1±20.0	336.2±20.1	337.1±21.4
Body weight	GD 22	406.0±18.5	407.1±25.3	400.6±25.0	403±28.2
Body weight gain	GD 1-22 [b]	121.5	126.8	122.2	126.5
Food consumption	Week 1	23.6±2.2	23.9±2.3	23.7±3.4	24.1±3.0
Food consumption	Week 2	27.3±1.9	27.9±2.0	27.4±4.7	27.0±2.5
Food consumption	Week 3	27.1±2.2	28.0±2.5	27.8±4.1	27.7±2.4
F1 Generation (F2a litter)					
Body weight	GD 1	261.0±23.2	263.1±17.6	265.3±19.3	268.1±22.2
Body weight	GD 8	291.4±21.9	293.8±16.8	296.6±21.4	300.4+21.4
Body weight	GD 15	318.2±23.1	319.9±18.7	320.8±19.8	328.7±23.1
Body weight	GD 22	373.8±24.5	374.1±24.3	370.7±26.7	378.8±20.3
Body weight gain	GD 1-22 [b]	112.8	111.0	105.4	110.7
Food consumption	Week 1	24.2±3.8	24.5±3.4	26.3±5.2	23.4±2.3
Food consumption	Week 2	25.0±3.4	25.5±3.8	25.0±3.2	25.1±2.7
Food consumption	Week 3	24.1±2.3	25.3±3.6	23.3±3.8	24.4±2.8
F1 Generation (F2b litter)					
Body weight	GD 1	303.5±23.5	310.1±16.4	307.0±23.1	304.8±19.8
Body weight	GD 8	327.4±21.7	334.7±14.8	330.2±24.8	324.6±23.7
	Adjusted	329.4	331.8	329.5	324.4*(↓2)
Body weight	GD 15	353.9±27.7	360.5±18.2	360.8±25.2	353.6±24.8
Body weight	GD 22	402.1±29.0	420.1±22.6	420.7±33.5	409.7±32.8
	Adjusted	405.9	414.8	420.5*(↑4)	408.1
Body weight gain	GD 1-22 [b]	98.6	110.0	113.7	104.9

a Data (n = 14-25) were obtained from Tables 16 through 17 and 24 through 25 on pages 81-83 and 99-100 of MRID 46800230. Percent differences from controls (calculated by reviewers) are included in parentheses.
b Calculated by the reviewers as the difference in unadjusted group mean body weights presented in this table.
* Significantly different from the control group at $p \leq 0.05$

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c. **Lactation:** There were no effects of treatment on body weights during lactation in either generation (Table 3c). Decreases (↓3-4%; $p \leq 0.05$) from controls noted in the 1500 ppm P dams on LD 15 and 22 and in the 50 and 1500 ppm F1 dams on LD 22 of the F2a litter were considered unrelated to treatment because they were minor, transient, and/or unrelated to dose. Body weights of the treated F1 dams were comparable to controls during lactation of the F2b litter. Body weight gains of the treated groups for the overall (LD 1-29) lactation period were comparable to controls in the P generation and in the F1 generation during the F2a and F2b litters. There were no effects of treatment on food consumption in the P or F1 dams during lactation.

TABLE 3c. Selected mean (∀SD) body weights (g), body weight gains (g), and food consumption (g/animal/day) during lactation [a]

Observation/study week		Dose Group (ppm)			
		0	50	250	1500
P Generation					
Body weight	LD 1	311.8±25.9	308.4±24.2	309.1±25.4	315.0±30.3
Body weight	LD 5	327.4±18.4	328.6±17.7	327.5±22.3	332.3±25.5
Body weight	LD 8	336.0±19.0	340.2±18.2	337.4±22.4	340.3±20.0
Body weight	LD 15	358.7±23.1	359.9±14.0	355.9±20.9	347.6±19.2
	Adjusted	359.0	357.6	355.7	347.5*(↓3)
Body weight	LD 22	356.1±23.2	354.6±19.3	351.9±18.2	344.6±20.8
	Adjusted	356.8	353.8	351.5	344.2**(↓4)
Body weight	LD 29	340.8±18.7	340.1±24.5	337.4±18.0	339.0±15.2
Body weight gain	LD 1-29 [b]	29.0	31.7	28.3	24.0
Food consumption	Week 1	39.5±8.4	39.7±10.3	41.2±10.6	39.4±6.2
Food consumption	Week 2	64.8±16.6	62.0±14.4	62.7±14.8	58.7±7.1
Food consumption	Week 3	83.3±19.6	78.0±19.1	78.9±17.2	75.3±9.1
Food consumption	Week 4	132.2±36.5	125.1±43.0	127.6±33.5	129.8±21.0
F1 Generation (F2a litter)					
Body weight	LD 1	274.1±22.2	285.1±19.2	272.5±27.3	288.2±28.2
Body weight	LD 5	296.2±20.3	304.0±16.9	299.1±30.1	308.6±23.1
Body weight	LD 8	320.1±19.2	319.3±21.3	319.9±28.3	319.8±21.2
Body weight	LD 15	339.3±21.4	339.1±18.5	341.4±25.6	336.4±19.4
Body weight	LD 22	342.9±22.5	339.8±16.4	342.6±22.0	338.6±18.8
	Adjusted	345.4	335.4*(↓3)	345.4	334.5*(↓3)
Body weight	LD 29	322.9±20.7	327.2±19.7	329.4±23.0	323.9±20.1
Body weight gain	LD 1-29 [b]	48.8	42.1	56.9	35.7
Food consumption	Week 1	38.2±8.0	35.2±6.2	35.5±7.8	34.4±5.1
Food consumption	Week 2	63.6±6.7	61.0±12.7	59.5±17.6	56.5±9.8
Food consumption	Week 3	81.6±8.9	77.9±10.6	75.5±20.5	73.1±18.0
Food consumption	Week 4	135.1±21.6	126.6±23.9	115.7±38.5*(↓14)	115.3±30.6
F1 Generation (F2b litter)					
Body weight	LD 1	316.4±22.9	328.5±23.7	325.0±29.5	309.1±29.8
Body weight	LD 5	333.6±20.2	344.5±26.8	343.7±27.4	335.8±23.9
Body weight	LD 8	348.4±24.8	354.1±23.8	359.1±27.7	352.1±22.1
Body weight	LD 15	357.6±23.3	368.2±18.1	371.7±26.3	365.6±21.0
Body weight	LD 22	356.8±29.7	364.9±15.8	370.3±23.6	363.9±19.0
Body weight	LD 29	343.0±26.8	348.9±24.3	356.5±26.7	344.2±22.5
Body weight gain	LD 1-29 [b]	26.6	20.4	31.5	35.1

a Data (n = 13-25) were obtained from Tables 18 through 19 and 26 through 27 on pages 84-86 and 101-102 of MRID 46800230. Percent differences from controls (calculated by reviewers) are included in parentheses.
b Calculated by the reviewers as the difference in unadjusted group mean body weights presented in this table.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

3. **Test substance intake:** Test substance intake (mg/kg/day) was calculated from the body weight and food consumption data, using the nominal concentration (ppm) of the diets. The mean test substance intake for both generations during pre-mating is considered to be representative of the achieved intake for the entire study (Table 4).

TABLE 4. Mean test substance intake (mg/kg/day in males/females) during pre-mating [a]

Generation	Dose (ppm)			
	0	50	250	1500
P generation	0/0	4.4/4.7	21.8/23.4	138.5/140.4
F1 generation	0/0	4.9/5.2	23.9/25.6	154.1/156.0
Mean [b]	**0/0**	**4.7/5.0**	**22.9/24.5**	**146.3/148.2**

a Data were obtained from Tables 4 and 5 on pages 51-52 of MRID 46800230.
b Calculated by the reviewers as the average of the P and F1 generations.

4. **Reproductive function**

a. **Estrous cycle length and periodicity:** There were no effects of treatment on the mean cycle duration, the mean number of cycles, or the percentages of animals having 3, 4, 5, or 6 cycles in either generation.

b. **Sperm measures:** In either generation, there were no treatment-related effects on sperm: (i) motility (as measured by straight line velocity, curvilinear velocity, average path velocity, percent straightness, or percent motile sperm); (ii) enumeration (as measured by the total sperm and the total sperm per gram tissue in the right cauda epididymis and in the right testis); or (iii) morphology (as measured by the percentages of normal sperm, abnormal sperm, sperm with abnormal head, sperm with abnormal tail, and sperm with multiple abnormalities). In the 1500 ppm P males, the weight of the right cauda epididymis was 6% higher ($p \leq 0.05$) than controls; however, both the total number of sperm and the number of sperm per gram right cauda were comparable to controls. Additionally, the percent of sperm with an abnormal shaped head at this dose (0.41%) was lower ($p \leq 0.01$) than controls (0.96%); however, this finding was not considered adverse.

5. **Reproductive performance:** There were no effects of treatment on the pre-coital interval, number of females pregnant, number of complete litter resorptions, mating success, post-implantation loss, or gestation duration in either generation (Table 5). There were no effects of treatment on whole litter losses in the P generation. However, in the F1 generation, the number of whole litter losses was increased in the F2a litter at 1500 ppm (5/23 [21.7%]) compared to controls (2/24 [8.3%]). Therefore, the F1 dams were mated a second time to produce the F2b litters, and there was no effect on the number of whole litter losses, indicating that the finding in the F2a litter was incidental.

TABLE 5. Reproductive performance [a]				
Parameter	Dose Group (ppm)			
	0	50	250	1500
P Generation (F1 litter)				
Pre-coital interval, mean ± SD days (n) [b]	2.38 ± 1.13 (24)	2.82 ± 2.70 (22)	2.20 ± 2.45 (25)	1.85 ± 0.92 (26)
# Females paired	26	26	26	26
# Pregnant [c]	25	21	25	22
# Failing to produce a litter	3	8	1	4
# Not pregnant [d]	1	5	1	4
# Complete litter resorption [e]	2	3	0	0
Successful mating (%) [f]	23/26 (88.5)	18/26 (69.2)	25/26 (96.2)	22/26 (84.6)
Post-implantation loss (%)	18/286 (6.3)	21/228 (9.2)	20/266 (7.5)	31/256 (12.1)
Implantations affected	5.8 ± 9.5	9.0 ± 11.0	9.2 ± 16.0	13.6 ± 19.8
Litters affected (%)	8/23 (34.8)	10/17 (58.8)	9/22 (40.9)	14/21 (66.7)
# Litters	23	18	25	22
Whole litter losses (%)	0/23 (0.0)	0/18 (0.0)	0/25 (0.0)	1/22 (4.5)
Gestation duration, mean ± SD days (n) [g]	22.3 ± 0.5 (22)	22.1 ± 0.6 (16)	22.1 ± 0.7 (24)	22.2 ± 0.4 (22)
F1 Generation (F2a litter)				
Pre-coital interval, mean ± SD days (n) [b]	2.19 ± 1.06 (26)	2.78 ± 1.31 (23)	2.76 ± 1.01 (25)	2.65 ± 2.77 (23)
# Females paired	26	26	26	26
Successful mating (%) [f]	24/26 (92.3)	24/26 (92.3)	25/26 (96.2)	22/26 (84.6)
# Litters	24	24	25	23
Whole litter losses (%)	2/24 (8.3)	1/24 (4.2)	2/25 (8.0)	5/23 (21.7)
Gestation duration, mean ± SD days (n) [g]	22.3 ± 0.6 (24)	22.1 ± 0.5 (23)	22.3 ± 0.5 (24)	22.3 ± 0.6 (20)
F1 Generation (F2b litter)				
Pre-coital interval, mean ± SD days (n) [b]	2.57 ± 2.60 (21)	3.17 ± 3.14 (23)	3.19 ± 3.16 (21)	1.88 ± 1.20 (16)
# Females paired [h]	22	24	22	19
Successful mating (%) [f]	17/22 (77.3)	18/24 (75.0)	15/22 (68.2)	15/19 (78.9)
# Litters	19	18	16	16
Whole litter losses (%)	3/19 (15.8)	1/18 (5.6)	1/16 (6.3)	1/16 (6.3)
Gestation duration, mean ± SD days (n) [g]	22.2 ± 0.8 (19)	21.9 ± 0.2 (17)	22.2 ± 0.7 (16)	22.2 ± 0.7 (14)

a Data were obtained from a text table and summary Tables 30 through 33 and 57 on pages 40, 105-110, and 207 of MRID 46800230.
b Number of days between the day of pairing and the day of positive vaginal smear
c Calculated by the reviewers as the difference in the number paired and the number not pregnant
d Number of dams with no implantation sites
e Number of dams with implantation sites present but failed to produce a litter
f Percent of dams producing a litter with at least one viable pup on LD 1
g Number of days between day of positive vaginal smear and LD 1 (in dams giving birth to at least one viable pup).
h Fewer animals were available for mating to produce the F2b litter because F1 animals had been removed from the study for investigation during production of the F2a litter (page 37 of study report).

6. Parental postmortem results

a. **Organ weights**: Absolute and adjusted (for terminal body weight) adrenal weights were increased by 13-23% ($p \leq 0.05$) at 1500 ppm compared to controls in the P males and F1 males and females (Table 6). Adrenal weights in the treated P females were comparable to controls. Absolute adrenal weights were also increased (↑11%; $p \leq 0.05$) in the 250 ppm F1 females. Additionally at 1500 ppm, absolute and adjusted liver weights were increased in the P males (↑17-19%) and females (↑7-8%) and in the F1 males and females (↑11-17%). These increases attained significance ($p \leq 0.05$) except for the absolute liver weight in the P females.

Additionally at 1500 ppm in the P generation, the following significant differences ($p \leq 0.05$) from controls were observed in organ weights, but were not considered to be an adverse effect of treatment because they were not corroborated by any macroscopic or microscopic lesions: (i) increased adjusted right cauda epididymis in the males (↑6%); (ii) increased absolute and adjusted kidney weights in both sexes (↑6-7%); (iii) increased absolute and adjusted ovary weights in the females (↑13-16%); (iv) decreased adjusted pituitary weight in the females (↓17%); and (v) increased absolute and adjusted thyroid weights in the males (↑23%).

In the F1 generation, the following organ weights were significantly increased ($p \leq 0.05$) over controls, but were not considered to be an adverse effect of treatment because they were not corroborated by any macroscopic or microscopic lesions: (i) adjusted brain weight in the ≥250 ppm males (↑2-4%); (ii) adjusted right cauda epididymis, right epididymis, and seminal vesicle weight in the 1500 ppm males (↑6-8%); (iii) adjusted kidney weights in the 1500 ppm males and females, and absolute kidney weights in the ≥250 ppm females (↑6-10%); and (iv) adjusted thyroid weight in the 1500 ppm males (↑10%).

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TABLE 6. Selected absolute and adjusted (for body weight) organ weights (g) [a]

Parameter	Dose Group (ppm)			
	0	50	250	1500
P generation Males				
Adrenal				
Absolute	0.064±0.012	0.066±0.010	0.069±0.014	0.072±0.014*(↑13)
Adjusted	0.064	0.066	0.069	0.072*(↑13)
Liver				
Absolute	23.8±3.2	24.4±2.7	24.4±3.2	27.9±4.2**(↑17)
Adjusted	23.7	23.8	24.8	28.2**(↑19)
P generation Females				
Adrenal				
Absolute	0.081±0.016	0.081±0.010	0.088±0.018	0.088±0.026
Adjusted	0.080	0.084	0.087	0.089
Liver				
Absolute	17.7±2.3	16.8±2.5	16.6±2.0	19.0±1.9(↑7)
Adjusted	17.6	17.0	16.7	19.0*(↑8)
F1 generation Males				
Adrenal				
Absolute	0.055±0.010	0.057±0.008	0.059±0.009	0.062±0.009**(↑13)
Adjusted	0.054	0.057	0.059	0.064**(↑19)
Liver				
Absolute	20.9±2.7	20.5±1.6	20.9±1.8	23.2±2.9**(↑11)
Adjusted	20.5	20.6	20.5	23.9**(↑17)
F1 generation Females				
Adrenal				
Absolute	0.082±0.012	0.088±0.014	0.091±0.016*(↑11)	0.101±0.022**(↑23)
Adjusted	0.082	0.088	0.091	0.101**(↑23)
Liver				
Absolute	16.7±3.5	17.7±4.3	18.3±3.8	19.4±3.3*(↑16)
Adjusted	16.7	17.9	17.7	19.6**(↑17)

a Data were obtained from Tables 49 and 50 on pages 153, 160, 172, and 179 of MRID 46800230.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

b. **Pathology**

1) **Macroscopic examination**: None of the macroscopic findings could be attributed to treatment.

2) **Microscopic examination**: An increased severity of vascular ectasia (Table 7) was observed in the 1500 ppm F1 females (8 dams with minimal to moderate severity) compared to controls (7 dams of minimal severity). However, vascular ectasia was only observed in 0-4 animals per group at 1500 ppm in the P generation males and females and in the F1 generation males. No other microscopic lesions could be attributed to treatment in either generation.

TABLE 7. Incidences (# animals affected) of vascular ectasia in the adrenal glands of the F1 parents [a]				
Parameter	Dose Group (ppm)			
	0	50	250	1500
P generation Males				
Adrenal gland – Number examined	26	8	2	26
Vascular ectasia, Total	4	1	0	3
P generation Females				
Adrenal gland – Number examined	26	26	26	26
Vascular ectasia, Total	3	0	1	2
Minimal	3	0	1	2
F1 generation Males				
Adrenal gland – Number examined	26	1	1	26
Vascular ectasia, Total	0	0	0	2
Minimal	0	0	0	2
F1 generation Females				
Adrenal gland – Number examined	20	22	20	19
Vascular ectasia, Total	7	5	6	8
Minimal	7	5	6	5
Slight	0	0	0	2
Moderate	0	0	0	1

a Data were obtained from Tables 58 and 59 on pages 208, 210, 215, and 218 of MRID 46800230.

B. OFFSPRING

1. **Viability and clinical signs**: Selected litter data are presented in Tables 8a and 8b. In the F2a litter, the live birth index was lower at 1500 ppm (86.8%) compared to controls (97.7%), and the litter size on PND 1 was decreased by 22% ($p \leq 0.01$) at 1500 ppm compared to controls. However, when the numbers of whole litter losses were excluded from the 1500 ppm (5/23) and control (2/24) groups, live birth index at the high dose (95.3%) was comparable to controls (97.8%). Data for mean litter size during the post-natal period were only presented excluding whole litter losses. Thus for the F2b litter, there was an apparent increase in the litter size that was attributed to the dams that were excluded because all of the pups in their litter died at some point during the post-natal period. There were no treatment-related clinical signs and no effects of treatment on anogenital distance.

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TABLE 8a. F1 Litter parameters [a]				
Parameter	Dose Group (ppm)			
	0	50	250	1500
F1 litter				
Mean (±SD) implantations (n)	12.4 ± 3.3 (23)	13.4 ± 4.6 (17)	12.1 ± 3.4 (22)	12.2 ± 2.4 (21)
Number born live	257	211	268	236
Number born dead [b]	11	8	2	3
Mean number born (live + dead)	11.7	12.2	10.8	10.9
Sex ratio (% males) PND 1	50.9 ± 20.6	54.3 ± 19.6	48.7 ± 14.3	50.7 ± 18.9
PND 29	49.3 ± 23.8	53.6 ± 22.3	48.9 ± 14.5	48.1 ± 16.6
Number deaths PND 1-29 [b, c]	14	33	9	6
Litter size [d] PND 1	11.2 ± 3.4	11.7 ± 4.2	10.7 ± 4.0	11.2 ± 2.6
PND 5	10.7 ± 3.8	9.9 ± 4.4	10.5 ± 3.9	11.0 ± 2.5
PND 8	10.7 ± 3.8	9.9 ± 4.4	10.4 ± 3.9	11.0 ± 2.4
PND 15	10.6 ± 3.8	9.9 ± 4.4	10.4 ± 3.9	11.0 ± 2.4
PND 22	10.6 ± 3.8	9.9 ± 4.4	10.4 ± 3.9	11.0 ± 2.4
PND 29	10.6 ± 3.8	9.9 ± 4.4	10.4 ± 3.9	11.0 ± 2.4
Birth index (%) [b, e]	94.4	91.0	89.3	89.3
Live Birth index (%) [f]	96.2 ± 10.9	97.1 ± 7.1	99.4 ± 1.9	98.7 ± 4.3
Viability index (%) [g]	93.4 ± 17.7	87.5 ± 25.3	97.5 ± 9.4	93.8 ± 21.2

a Data were obtained from Tables 34 through 36, 38, 39, and 57 on pages 111-115, 122, 123, 128, 129, and 207 of MRID 46800230.
b Calculated by the reviewers
c Includes pups born dead
d The only data available for litter size excluded whole litter losses.
e Birth index = mean # born (live + dead) / mean # implantations x 100
f Live birth index = # born live/ # born x 100
g Viability index = # alive on PND 29/ # born x 100

TABLE 8b. F2 Litter parameters [a]

Parameter		Dose Group (ppm)			
		0	50	250	1500
F2a litter					
Number born live		305	255	305	208
Number born dead [b]		7	21	28	29
Sex ratio (% males)	PND 1	53.5 ± 16.7	54.6 ± 21.6	46.2 ± 10.5	63.7 ± 20.6
	PND 29	51.1 ± 15.8	53.0 ± 19.5	48.0 ± 16.7	59.4 ± 24.9
Number deaths	PND 1-29 [b, c]	57	10	82	42
Litter size [d]	PND 1	12.6 ± 2.3	11.0 ± 3.1	12.5 ± 2.8	9.8 ± 3.4** (↓22)
	PND 5	11.3 ± 2.3	10.8 ± 3.0	9.5 ± 4.2	9.2 ± 3.5
	PND 8	11.3 ± 2.3	10.7 ± 2.9	9.5 ± 4.2	9.2 ± 3.5
	PND 15	11.3 ± 2.3	10.7 ± 2.9	9.5 ± 4.2	9.2 ± 3.5
	PND 22	11.3 ± 2.3	10.7 ± 2.9	9.5 ± 4.2	9.2 ± 3.5
	PND 29	11.3 ± 2.3	10.7 ± 2.9	9.5 ± 4.2	9.2 ± 3.5
Live Birth index (%),	including [d, e]	97.7 ± 4.2	93.7 ± 19.0	92.9 ± 16.2	86.8 ± 26.2*
	excluding [d, e]	97.8 ± 4.3	97.5 ± 4.4	95.6 ± 8.1	95.3 ± 12.1
Viability index (%) [f]		83.0 ± 29.8	93.0 ± 20.9	71.8 ± 37.0	77.2 ± 39.7
F2b litter					
Number born live		160	199	183	195
Number born dead [b]		24	2	6	20
Sex ratio (% males)	PND 1	60.9 ± 20.2	51.8 ± 20.0	49.5 ± 12.9	55.8 ± 12.5
	PND 29	62.7 ± 19.5	49.9 ± 16.6*	49.3 ± 13.1*	53.5 ± 15.0
Number deaths	PND 1-29 [b, c]	9	6	16	19
Litter size [d]	PND 1	9.6 ± 3.8	11.6 ± 2.9* (↑21)	12.2 ± 1.9** (↑27)	13.0 ± 2.1** (↑35)
	PND 5	9.4 ± 3.6	11.1 ± 2.6	11.3 ± 2.0	11.9 ± 3.1* (↑27)
	PND 8	9.4 ± 3.6	11.1 ± 2.6	11.3 ± 2.0	11.9 ± 3.1* (↑27)
	PND 15	9.4 ± 3.6	11.1 ± 2.6	11.2 ± 1.9	11.8 ± 3.1* (↑26)
	PND 22	9.4 ± 3.6	11.1 ± 2.6	11.1 ± 1.8	11.7 ± 3.0* (↑24)
	PND 29	9.4 ± 3.6	11.1 ± 2.6	11.1 ± 1.8	11.7 ± 3.0* (↑24)
Live Birth index (%)		86.1 ± 31.8	99.3 ± 2.9	93.4 ± 24.9	91.9 ± 24.9
Viability index (%) [f]		92.8 ± 24.2	91.7 ± 24.6	92.5 ± 14.8	91.0 ± 19.0

a Data were obtained from Tables 34 through 36, 38, 40, on pages 111-115, 124-127, 130-133, of MRID 46800230.
b Calculated by the reviewers
c Includes pups born dead
d The only data available for litter size excluded whole litter losses. Live birth index is presented both including and excluding whole litter losses for the F2a litter because of an observed equivocal increase in this parameter in F2a litter. All other data presented include whole litter losses.
e Live birth index = # born live/ # born x 100
f Viability index = # alive on PND 29/ # born x 100
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

2. **Body weight:** At 1500 ppm, adjusted (for initial body weight) pup weights were decreased ($p \leq 0.05$) by 7-12% in the F1 males and females and by 11-14% in the F2b males and females (Tables 9a and 9b). In the F2a litter, pup weights of the treated males and females were comparable to controls. There were no effects of treatment on total litter weight (Table 9c). Total litter weights were comparable to controls in the F1 litter. In the F2a litter, total litter weights were decreased by 18-23% ($p \leq 0.05$) in the 250 and 1500 ppm groups generally

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throughout the post-natal period. Because pup weights in these groups were comparable to controls, it is likely that these decreases are attributable to the slightly lower numbers of pups in these groups, with a mean of 9.2-9.5 pups in the 250 and 1500 ppm groups compared to 11.3 in the controls (Table 8b). In the F2b litter, total litter weights were not decreased, although an incidental increase of 22-31% ($p \leq 0.05$) was noted at 250 and 1500 ppm on PND 1. Because the decreases in total litter weight noted in the F2a litters were not reproduced in the F2b litters, these findings were considered unrelated to treatment.

TABLE 9a. Mean (∀SD) absolute and adjusted (for initial body weight) pup weights (g) [a]

Post-natal day (PND)	Dose Group (ppm)			
	0	50	250	1500
F1 Male Pups				
1	6.1±0.7	6.1±0.9	6.3±0.7	6.4±0.7
5	10.3±1.3	10.3±1.8	10.6±1.9	10.3±1.7
8	15.1±1.9	15.0±2.4	15.3±3.1	14.9±2.7
15	28.5±3.6	29.0±4.3	29.0±5.3	26.5±4.6
adjusted	28.7	29.6	28.5	25.9**(↓10)
22	46.3±6.2	46.9±6.6	47.0±8.0	42.2±7.0
adjusted	46.9	47.8	46.3	41.3**(↓12)
29	86.0±9.2	86.1±10.7	86.6±12.0	78.4±10.9
adjusted	87.0	87.7	85.5	77.1**(↓11)
F1 Female Pups				
1	5.8±0.7	5.6±0.8	6.1±0.7	5.9±0.5
5	9.6±1.5	9.3±1.8	10.3±1.9	9.8±1.4
8	13.9±2.2	13.7±2.5	14.9±3.0	14.2±2.4
15	26.9±4.1	27.0±3.8	28.4±5.6	25.8±4.8
adjusted	27.3	28.1	27.3	25.3*(↓7)
22	44.0±6.2	44.3±5.8	45.8±8.3	40.6±6.5
adjusted	44.7	46.1	44.2	39.6**(↓11)
29	79.0±8.6	79.3±9.2	81.5±12.3	73.5±9.6
adjusted	80.2	82.0	79.2	72.2**(↓10)

a Data were obtained from Table 44 on pages 142-143 of MRID 46800230.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

TABLE 9b. Mean (∀SD) pup weights (g) [a]				
Post-natal day (PND)	Dose Group (ppm)			
	0	50	250	1500
F2a Male Pups				
1	5.8±0.7	6.0±0.7	5.5±0.8	5.9±0.9
5	9.3±1.6	9.9±1.5	9.0±1.3	10.1±1.9
8	13.6±1.8	14.0±2.0	13.3±1.9	14.3±2.6
15	26.8±2.6	27.0±3.2	26.4±3.6	26.8±4.3
22	43.4±4.6	43.4±5.1	42.7±6.4	43.7±7.6
29	81.4±7.6	80.9±8.0	80.6±9.1	81.3±12.0
F2a Female Pups				
1	5.5±0.6	5.8±0.7	5.2±0.7	5.7±1.0
5	9.1±1.3	9.4±1.4	8.5±1.3	9.6±1.9
8	13.3±1.5	13.5±2.0	12.5±1.9	13.6±2.6
15	26.4±2.5	26.1±3.2	25.5±3.3	25.9±4.4
22	42.5±4.3	41.7±4.8	42.0±5.7	42.4±7.3
29	76.7±6.6	75.4±6.6	75.6±8.1	76.8±10.3
F2b Male Pups				
1	6.5±1.1	6.2±0.8	6.0±0.7	6.0±1.0
5	10.7±1.9	9.9±1.3	10.0±0.8	9.6±1.7
8	16.1±2.4	14.4±1.8	14.5±1.4	14.0±2.2
15	30.7±3.9	27.6±3.1	28.3±2.2	25.3±3.9
adjusted	29.9	27.9	28.6	25.7**(↓14)
22	49.8±6.2	45.2±4.7	46.8±3.8	42.0±6.2
adjusted	48.3	45.7	47.3	42.5**(↓12)
29	89.9±10.1	82.8±9.4	84.7±6.2	76.7±10.9
adjusted	87.1	83.3	85.9	77.2**(↓11)
F2b Female Pups				
1	6.0±1.1	5.6±0.9	5.7±0.7	5.6±0.8
5	9.9±1.9	9.2±1.4	9.5±1.0	8.9±1.6
8	15.0±2.3	13.5±1.9	14.2±1.6	13.3±2.2
15	29.3±3.6	26.2±3.1	27.3±2.4	24.5±3.6
adjusted	28.8	26.6*(↓8)	27.5	24.9**(↓14)
22	47.6±6.1	43.2±5.0	44.5±4.3	40.3±5.9
adjusted	46.5	44.0	44.6	40.5**(↓13)
29	83.7±9.3	76.5±9.5	80.2±6.1	71.2±9.6
adjusted	81.2	77.4	80.7	71.7**(↓12)

a Data were obtained from Table 45 on pages 144-147 of MRID 46800230.

** Significantly different from the control group at p≤0.01

TABLE 9c. Mean (∀SD) litter weights (g) [a]

Post-natal day (PND)	Dose Group (ppm)			
	0	50	250	1500
F1 Litter				
1	65.7±18.3	66.1±19.9	64.0±21.3	64.9±18.0
5	105.3±34.0	95.8±39.9	104.1±29.8	107.2±18.9
8	152.5±48.4	140.2±57.9	147.8±41.4	153.8±25.1
15	288.0±89.7	270.1±106.9	278.2±78.0	277.1±43.9
22	468.9±144.7	437.6±169.2	453.0±129.6	439.9±75.1
29	860.9±270.1	801.7±320.1	828.6±250.4	812.3±145.2
F2a Litter				
1	70.6±10.1	62.2±18.3	63.8±16.2	54.1±20.8**(↓23)
5	104.2±25.1	102.2±23.0	82.6±35.6*(↓21)	87.1±26.4
8	151.7±33.5	144.8±31.1	119.2±48.7**(↓21)	123.7±37.1*(↓18)
15	297.1±53.6	278.0±57.2	236.7±92.0**(↓20)	233.9±65.6*(↓21)
22	478.7±82.9	445.1±90.1	384.5±145.6**(↓20)	380.7±104.1*(↓20)
29	885.0±165.2	823.1±178.9	719.2±281.1*(↓19)	707.2±208.4*(↓20)
F2b Litter				
1	57.5±21.5	63.1±19.0	70.4±8.4*(↑22)	75.5**±11.5(↑31)
5	91.5±35.0	104.7±24.6	109.0±17.6	109.6±29.2
8	142.1±42.1	154.2±35.4	160.6±25.3	161.4±40.7
15	274.8±82.6	298.3±66.4	308.6±40.2	289.6±63.2
22	443.4±146.2	490.7±109.4	504.3±67.4	475.1±106.0
29	802.5±258.1	882.8±198.5	912.3±130.2	855.3±194.7

a Data were obtained from Table 46 on pages 148-150 of MRID 46800230.
* Significantly different from the control group at p≤0.05
** Significantly different from the control group at p≤0.01

3. **Sexual maturation**: In the F1 parental males, the time until preputial separation was longer (p≤0.05) at 1500 ppm (44.8 days) compared to controls (43.7 days), indicating a slight delay in sexual maturation likely related to the decreased pup body weights beginning on PND 15. However, the time to vaginal opening was unaffected by treatment. Although there were more females with vaginal opening occurring on PND 36 at 1500 ppm (23.1%) compared to controls (0%), the mean number of days until vaginal opening in the treated groups (33.8-34.5 days) was comparable to controls (34.1 days). The body weights at criterion were similar across all groups for both sexes.

4. **Offspring postmortem results**

a) **Organ weights**: At 1500 ppm, adjusted (for terminal body weight) liver weights were increased (p≤0.01) by 9-17% in the F1, F2a, and F2b pups, and absolute liver weights were increased (p≤0.01) by 14% in the F2a females (Table 10). Additionally at this dose, the following organ weights were increased (p<0.05), but were considered incidental to treatment and were likely related to the decreased terminal body weight: (i) increased adjusted brain weight in the F1 pups of both sexes and in the F2a males (↑3%); (ii) decreased absolute spleen weight in the F2b females (↓19%); and (iii) decreased absolute thymus weight in the

F2b females (↓12%).

TABLE 10. Mean (∀SD) liver weights (g) [a]

Parameter	Dose Group (ppm)			
	0	50	250	1500
F1 Males				
Absolute	4.52±0.72	4.55±0.78	4.49±0.95	4.40±0.85
Adjusted	4.38	4.46	4.37	4.76**(↑9)
F1 Females				
Absolute	4.12±0.51	4.17±0.69	4.28±0.81	4.25±0.67
Adjusted	4.10	4.13	4.07	4.50**(↑10)
F2a Males				
Absolute	4.47±0.59	4.52±0.74	4.16±0.65	4.85±1.01(↑9)
Adjusted	4.41	4.51	4.22	4.86**(↑10)
F2a Females				
Absolute	4.04±0.68	4.00±0.52	3.96±0.59	4.62±0.67**(↑14)
Adjusted	4.08	4.07	3.93	4.50**(↑10)
F2b Males				
Absolute	4.69±0.50	4.56±0.71	4.51±0.54	4.63±0.93
Adjusted	4.31	4.54	4.51	5.04**(↑17)
F2b Females				
Absolute	4.49±0.71	4.22±0.71	4.33±0.59	4.23±0.89
Adjusted	4.14	4.26	4.15	4.59**(↑11)

a Data were obtained from Tables 61 through 63 on pages 225, 229, and 233 of MRID 46800230.
** Significantly different from the control group at p≤0.01

b) Pathology

1) **Macroscopic examination:** There were no treatment-related macroscopic findings in the F1, F2a, or F2b pups.

2) **Microscopic examination:** Not determined

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS= CONCLUSIONS:** It was concluded that the LOAEL for the parents and offspring was 1500 ppm based on decreases in food utilization efficiency and body weights. Additionally, the liver was identified as a target organ because liver weights were increased at this dose in both generations, in parents and in the pups. The NOAEL for parental and offspring toxicity was 250 ppm. There were no effects on any reproductive parameter; thus the LOAEL for reproductive toxicity was not observed, and the NOAEL was 1500 ppm.

B. REVIEWER COMMENTS

1. **PARENTAL ANIMALS:** There were no effects of treatment on parental mortality, clinical signs, estrous cycle duration or periodicity; sperm parameters, or gross pathology. Additionally, there were no treatment-related effects on body weights, body weight gains, food consumption, or food utilization during gestation or lactation.

During pre-mating in the P generation, food consumption was increased by 5-10% ($p \leq 0.05$) in the 1500 ppm males during Weeks 1-4, while body weights were comparable to controls. Because these animals were eating more food to maintain the same body weight, food utilization was decreased ($p \leq 0.05$) by 8% during Weeks 1-4, resulting in decreased (↓4%; $p \leq 0.01$) food utilization for the overall (Weeks 1-10) pre-mating period.

At 1500 ppm in the F1 generation, body weights were decreased by 2-8% in the males throughout pre-mating, attaining significance ($p \leq 0.05$) in 7 of 11 weeks. Weekly cumulative body weight gains in these animals were decreased by 6-9% ($p \leq 0.05$) throughout pre-mating, resulting in a decrease of 6% in body weight gain for the overall (Weeks 1-11) pre-mating period. Food consumption in these males was decreased by 5% during Weeks 9-10, and food utilization was decreased by 8% ($p \leq 0.01$) during Weeks 1-4 and by 6% ($p \leq 0.05$) during Weeks 5-8, resulting in a decrease of 4% ($p \leq 0.01$) for overall (Weeks 1-10) food utilization.

In the 1500 ppm F1 females, food utilization was comparable to controls during pre-mating. Thus, the increases in body weights and body weight gains observed in these dams were not considered adverse and may have been due to the increased food consumption.

At 1500 ppm, absolute and adjusted liver weights were increased in the P males (↑17-19%) and females (↑7-8%) and in the F1 males and females (↑11-17%). These increases attained significance ($p \leq 0.05$) except for the absolute liver weight in the P females. Because there were no microscopic findings in the liver and clinical chemistry analyses were not performed, the increased liver weights were considered equivocal in this study. Similar findings in the liver were noted in the subchronic (MRID 46800216) and combined chronic/oncogenicity (MRID 46800234) studies in rats, submitted concurrently. In the subchronic toxicity study in rats (MRID 46800216), indications of slight hepatotoxicity were observed at 3000 and 5000 ppm, including increases ($p \leq 0.01$) in GGT (↑58-105%) in the males and in absolute and adjusted (for body weight) liver weights (↑14-36%) in both sexes. Additionally, minimal to slight eosinophilia in the liver was noted in the 5000 ppm males (8/10) and the 3000 and 5000 ppm females (10/10 each treated) vs 0/10 in the controls and other dose groups. In the combined chronic toxicity/oncogenicity study in rats (MRID 46800234), Slight increases (↑10-14%; $p \leq 0.05$) in adjusted liver weight were observed at Week 53 in the 1000 ppm males and in the 250 and 1000 ppm females and at Week 104 in the 1000 ppm females. However, an adverse effect was not corroborated by clinical chemistry or pathological tissue examination.

Absolute and adjusted adrenal weights were increased by 13-23% ($p \leq 0.05$) at 1500 ppm compared to controls in the P males and F1 males and females. Absolute adrenal weights

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were also increased (↑11%; p≤0.05) in the 250 ppm F1 females. An increased severity of vascular ectasia was observed in the 1500 ppm F1 females (8 dams with minimal to moderate severity) compared to controls (7 dams of minimal severity). However, vascular ectasia was only observed in 0-4 animals per group at 1500 ppm in the P generation male and females and in the F1 generation males. The Sponsor stated that vascular ectasia in the adrenal is a common spontaneous age-related lesion seen predominantly in female rats. It was also stated that no age-appropriate historical control data were available, but that the severity and incidence observed in the 1500 ppm F1 dams is within the historical control maximum for 1 year interim sacrifice. Although data were not available, it was stated that the incidence of this finding can be as high as 90% at one year and varies widely, along with severity. Therefore, the findings in the adrenal gland were considered to be equivocal.

The LOAEL for parental toxicity is 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females) based on decreased body weights, body weight gains, food consumption, and food utilization in the males. The NOAEL is 250 ppm (equivalent to 22.9/24.5 mg/kg/day in males/females).

2. **<u>OFFSPRING</u>:** There were no treatment-related effects on viability, clinical signs, or anogenital distance. In the F2a litter, the live birth index was lower at 1500 ppm (86.8%) compared to controls (97.7%), and the litter size on PND 1 was decreased by 22% (p≤0.01) at 1500 ppm compared to controls. However, when the numbers of whole litter losses were excluded, these effects were not evident.

   At 1500 ppm, adjusted pup weights were decreased (p≤0.05) by 7-14% in the F1 and F2b pups of both sexes. In the F2a litter, pup weights of the treated males and females were comparable to controls. There were no effects of treatment on total litter weight.

   In the F1 parental males, the time until preputial separation was longer (p≤0.05) at 1500 ppm (44.8 days) compared to controls (43.7 days), indicating a slight delay in sexual maturation likely related to the decreased pup body weights beginning on PND 15. However, the time to vaginal opening was unaffected by treatment.

   At 1500 ppm, adjusted (for terminal body weight) liver weights were increased by 9-17% in the F1, F2a, and F2b pups. Additionally at this dose, absolute liver weights were increased by 14% in the F2a females. However, because no clinical chemistry or histopathology analyses were performed, the increased liver weights were considered equivocal.

   The LOAEL for offspring toxicity 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females) based on decreased pup body weights in both sexes. The NOAEL is 250 ppm (equivalent to 22.9/24.5 mg/kg/day in males/females).

3. **<u>REPRODUCTIVE TOXICITY</u>:** There were no effects of treatment on the pre-coital interval, number of females pregnant, number of complete litter resorptions, mating success, post-implantation loss, or gestation duration in either generation. There were no effects of treatment on whole litter losses in the P generation. However, in the F1 generation, the number of whole litter losses was increased in the F2a litter at 1500 ppm compared to

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controls. Therefore, the F1 dams were mated a second time to produce the F2b litters, and there was no effect on the number of whole litter losses, indicating that the finding in the F2a litter was incidental.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 1500 ppm (equivalent to 146.3/148.2 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

C. <u>STUDY DEFICIENCIES</u>: No historical control data were provided. However, this deficiency was considered minor because it did not affect the conclusions of this DER. There were no other study deficiencies.

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APPENDIX

In a one-generation reproduction toxicity study (MRID 46800231), Mandipropamid (96.5%; Batch # SEZ2BP007) was administered in the diet to 14 Alpk:AP$_f$SD (Wistar-derived) rats/sex/dose group at dose levels of 0, 250, 500, 1500, or 3000 ppm. The P generation animals were fed the test diets for 9-10 weeks prior to mating to produce the F1 litters. The P dams were allowed to rear the F1 offspring to weaning.

At 1500 and 3000 ppm in the P generation, food consumption was increased by 8-18% ($p \leq 0.05$) in the males during Weeks 1-4. Food utilization in these animals was decreased by 7-19% ($p \leq 0.05$) for Weeks 1-3, 4-6, and the overall (Weeks 1-9) pre-mating period. Body weights in the dams at these doses were decreased by 4-7% ($p \leq 0.05$) on lactation day (LD) 22. Absolute and adjusted liver weights were increased by 9-26% ($p \leq 0.05$) in both sexes. However, no treatment-related macroscopic findings were noted, and microscopic analyses were not performed.

Additionally at 3000 ppm in the P generation, body weights and body weight gains were decreased by 3-10% ($p \leq 0.05$) in the males beginning at Week 3 and continuing throughout the remainder of the pre-mating period. Several reproductive organs differed significantly ($p \leq 0.05$) from controls at this dose, including increased seminal vesicles, and decreased weights of the epididymides, testes and ovaries. However, these differences were not considered adverse because there were no effects on any reproductive parameters.

The LOAEL for parental toxicity is 1500 ppm (equivalent to 144.9/145.0 mg/kg/day in males/females) based on decreased food utilization. The NOAEL is 500 ppm (equivalent to 47.1/49.5 mg/kg/day in males/females).

In the pups at 3000 ppm, body weights were decreased by 13-25% ($p \leq 0.05$) beginning on post-natal day (PND) 8 and continuing throughout the remainder of the post-natal period to weaning. It was stated that because there was no evidence of decreased pup body weights at birth or early lactation, the decreased pup weights at the end of lactation were due to toxicity from the pups starting to eat the test diets.

The LOAEL for offspring toxicity is 3000 ppm (equivalent to 307.0/298.2 mg/kg/day) based on decreased pup body weights. The NOAEL is 1500 ppm (equivalent to 144.9/145.0 mg/kg/day in males/females).

There were no effects of treatment on reproductive performance.

The LOAEL for reproductive toxicity was not observed. The NOAEL is 3000 ppm (equivalent to 307.0/298.2 mg/kg/day).

This range-finding study is classified as an **acceptable/non-guideline** one-generation reproduction toxicity study in the rat.

<u>COMPLIANCE</u>: Signed and dated Data Confidentiality, GLP Compliance, and Flagging statements were provided.